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# Colchicine for prevention of vascular inflammation in Non-CardioEmbolic stroke (CONVINCE) – study protocol for a randomised controlled trial

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## Abstract

**Background:** Inflammation contributes to unstable atherosclerotic plaque and stroke. In randomised trials in patients with coronary disease, canukinumab (an interleukin-1B antagonist) and colchicine (a tubulin inhibitor with pleiotropic anti-inflammatory effects) reduced recurrent vascular events.

Hypothesis: Anti-inflammatory therapy with low-dose colchicine plus usual care will reduce recurrent vascular events in patients with non-severe, non-cardioembolic stroke and TIA compared with usual care alone.

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**Design:** CONVINCE is a multi-centre international (in 17 countries) Prospective, Randomised Open-label, Blinded-Endpoint assessment (PROBE) controlled Phase 3 clinical trial in 3154 participants. The intervention is colchicine 0.5 mg/day and usual care versus usual care alone (antiplatelet, lipid-lowering, antihypertensive treatment, lifestyle advice). Included patients are at least 40 years, with non-severe ischaemic stroke (modified Rankin score $\leq$3) or high-risk TIA (ABCD2 $>$ 3, or positive DWI, or cranio-cervical artery stenosis) within 72 hours-28 days of randomisation, with qualifying stroke/TIA most likely caused by large artery stenosis, lacunar disease, or cryptogenic embolism. Exclusions are stroke/TIA caused by cardio-embolism or other defined cause (e.g. dissection), contra-indication to colchicine (including potential drug interactions), or incapacity for participation in a clinical trial. The anticipated median follow-up will be 36 months. The primary analysis will be by intention-to-treat.
**Outcome:** The primary outcome is time to first recurrent ischaemic stroke, myocardial infarction, cardiac arrest, or hospitalisation with unstable angina (non-fatal or fatal).
**Summary:** CONVINCE will provide high-quality randomised data on the efficacy and safety of anti-inflammatory therapy with colchicine for secondary prevention after stroke.
**Schedule:** First-patient first-visit was December 2016. Recruitment to complete in 2021, follow-up to complete in 2023.

**Keywords**
Ischaemic stroke, inflammation, colchicine, randomised controlled trial

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## Introduction

Despite optimal medical care, the residual risk of recurrent vascular events remains high in survivors of non-severe ischaemic stroke. A recent systematic review reported annual rates of recurrent stroke and myocardial infarction of approximately 6% in survivors of first stroke or transient ischaemic attack (TIA), corresponding to about 1 in 4 patients at 5 years.[1] One-third of these events were fatal. Recurrent stroke also causes greater disability and dementia compared with first-ever stroke. Therefore, there is a great need as well as opportunity to decrease the risk of recurrent vascular events in stroke survivors.

Atherosclerosis is a major contributor to ischaemic stroke and an attractive treatment target because of its role in stroke pathophysiology and because several atherosclerosis risk factors are modifiable. Carotid or vertebral artery stenosis and intracranial atherosclerosis are detected in 20–30% of symptomatic patients.[2,3] Athero-thrombosis is also present in a substantial proportion of the 30–40% of patients with cryptogenic or embolic stroke of undetermined origin (ESUS).[4] For example, 73% of patients in the North Dublin Population Stroke Study with TOAST-classified stroke of unidentified etiology had evidence of aortic or cranio-cervical atherosclerosis defined by the ASCO classification.[5] In studies of prolonged cardiac monitoring in cryptogenic stroke, only 9–18% had evidence of paroxysmal atrial fibrillation at 1 year, suggesting that embolism from atherosclerotic plaque is likely to be an important mechanism of ESUS.[6–8] In lacunar stroke, micro-atheroma of larger penetrating arterioles is known to be an important mechanism. In the SPARCL trial, which targeted atherosclerosis with intensive lipid-lowering therapy, no heterogeneity in treatment effect was observed in patients with lacunar stroke,[9] suggesting that anti-atherosclerotic therapy is beneficial in lacunar stroke

Biomarker, genetic epidemiology, pathological, and imaging studies with positron-emission tomography support an association of inflammation with coronary events and stroke.[10] Inhibition of plaque inflammation is a promising therapeutic target to prevent recurrent vascular events. The CANTOS trial recently reported a significant reduction in risk of vascular events in patients with coronary disease treated with canukinumab, an interleukin-1$\beta$ antagonist.[11] However, because patients with stroke were excluded from CANTOS and safety concerns persist with canukinumab, other anti-inflammatory strategies require investigation.

Colchicine is a potent inhibitor of microtubule function, and inhibits inflammasome assembly, interleukin 1–$\beta$ activation, inflammatory cell mitosis and motility.[12,13] In two randomised trials in patients with coronary disease, low-dose colchicine reduced recurrent vascular events with an acceptable safety profile.[14,15] In a recent meta-analysis of randomised trials in coronary patients, colchicine reduced stroke outcomes despite inclusion of few patients with a qualifying stroke event.[16] CONVINCE is a secondary stroke prevention trial investigating the efficacy of

anti-inflammatory therapy with low-dose colchicine for secondary vascular prevention after ischaemic stroke/TIA (Figure 1).[17] We hypothesise that low-dose daily colchicine in addition to guideline-based usual care will reduce first recurrent stroke and coronary events (fatal and non-fatal) after non-severe non-cardioembolic stroke or high-risk TIA, compared to usual care alone.

## Design and methods

### Overview

CONVINCE is an investigator-led parallel-group Prospective, Randomised Open-label, Blinded-Endpoint assessed (PROBE) controlled Phase 3 clinical trial. Funding agencies are the Health Research Board of Ireland, German Research Foundation, and FWO Belgium. The trial project office is based in the HRB Stroke Clinical Trials Network Ireland at University College Dublin, with additional coordinating clinical trials units at University of Central Lancashire (United Kingdom), University of Essen (Germany), and Leuven University (Belgium). One hundred and fifty sites in 17 countries (16 European and Canada) are collaborating (Figure 2). Trial governance consists of a Steering Committee with independent chairperson, Data Monitoring Committee, and Project Management Group. A Lead Investigator represents each participating country on the Steering Committee.

After a 12-month preparatory period, the first patient was randomised in December 2016. An initial internal pilot phase (Vanguard Phase) with a pre-determined sample size of 265 patients was conducted to evaluate recruitment assumptions, study drug tolerability, and to refine study procedures. Following review of the trial progress at the end of the Vanguard Phase (in mid-2018) by the Steering and Data Monitoring Committees, the trial proceeded to the Full Trial phase in 2018. No interim efficacy analysis or 'spending of p values' was done at this review. Recruitment is scheduled to finish in 2021 with follow-up and close-out to be completed in 2023.

### Study procedures

Inclusion and exclusion criteria are summarised in Table 1 and the Web-supplement. Clinically-stable patients aged at least 40 years, with non-severe ischaemic stroke or high-risk TIA within the previous 28 days of randomisation, in whom the qualifying event was most likely caused by large artery stenosis, lacunar disease, or cryptogenic embolism are eligible. Main exclusion criteria are stroke due to cardio-embolism or other defined causes (e.g. arterial dissection), pre-existing neuromuscular, liver, renal, blood or gastro-intestinal disorders, or use of medications which may interact with colchicine. Following verification of eligibility and informed consent by the patient, randomisation to low-dose colchicine plus usual care or to usual care alone is done, via a web-based computerised system. A minimisation algorithm is used, to ensure groups are balanced for key prognostic variables. Minimisation variables are age (<70 years or 70 or greater), time since qualifying event (7 days or less; greater than 7 days), type of qualifying event (stroke or TIA), and presence of large-artery stenosis (if available).

The study schedule comprises the Baseline Visit and Follow-Up Visits at 28 and 90 days (telephone visit), and every 6 months after. At the baseline visit, key demographic, clinical, imaging, and laboratory characteristics are recorded. Quality of life is measured using the EQ5D questionnaire and cognition measured using the Montreal Cognitive Assessment (MOCA). At follow-up visits, patients are assessed for pulse and blood pressure, modified Rankin score, outcome events, adverse events, compliance, and use of concomitant medications. Blood tests for serum B12 and C-reactive protein are measured at 28 days, and repeated annually with other safety monitoring laboratory tests (blood count, renal, and liver profiles). EQ5D and MOCA assessments are repeated at the 6th follow-up visit (Year 2) and/or end-of-trial visit. The protocol allows follow-up visits to be conducted by telephone with the patient or a surrogate, if an in-person visit is not possible. Data is entered into an electronic case-report form (eCRF) and securely stored on servers at the trial Data Management Unit (Clinical Research Facility Galway).

The trial intervention is colchicine 0.5 mg daily in addition to usual guideline-based care (antiplatelet, lipid-lowering, antihypertensive therapy and lifestyle advice). The control arm consists of usual care only, with patients advised to avoid regular colchicine treatment. Study medication is purchased from a central supplier, re-labelled to comply with national and European Union regulations, and shipped to sites from central hubs. Patients randomised to colchcine are instructed to take a single tablet daily, while avoiding contra-indicated medications and grapefruit juice. Compliance is measured by remaining pill counts at follow-up visits and further education is provided if non-compliance is identified. If a contra-indicated medication is required for a short period (e.g. clarithromycin), the patient is requested to stop colchicine for the duration of therapy, followed by a 7-day washout period and resumption of colchicine.

### Outcomes

The primary outcome is time to non-fatal recurrent ischaemic stroke, myocardial infarction, cardiac arrest, hospitalisation for unstable angina or vascular

death. Transient focal symptoms with acute ischaemic change on brain imaging, retinal infarction, and spinal infarction are included in the definition of outcome stroke. Myocardial infarction is defined according to the 3rd Universal Definition of Myocardial Infarction.[18] Unstable angina requiring hospitalisation is defined using the Thrombolysis in Myocardial Infarction (TIMI) investigators definition. Vascular death is defined as death within 30 days following a recurrent event. All outcomes are assessed by an independent Adjudication Committee, comprising stroke physicians and cardiologists blinded to the treatment assignment.

Secondary outcomes are individual components of the primary outcome, fatal and non-fatal stroke combined, disability (measured by modified Rankin score), and pre-specified safety measures. Health economic outcomes will include overall costs of healthcare related to outcome events and quality-adjusted life years in treatment and control arms. Pre-specified exploratory outcomes are cognition (measured by Montreal Cognitive Assessment), difference in C-reactive protein, quality-of-life, and cumulative number of recurrence events in each study arm.

## Safety

An enhanced safety monitoring strategy is in place for CONVINCE. Site investigators are trained at trial initiation visits to assess patients and report pre-specified adverse events relating to gastro-intestinal, liver, renal, blood, metabolic (low serum B12), skin, neuromuscular, infectious disease, cancer, and bleeding. Screening laboratory tests for blood, liver, and renal dysfunction, and for serum B12 deficiency, are done at trial entry and annually. Adverse events are reported in the eCRF and those meeting criteria for Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions are reported within 24 hours to the trial Pharmacovigilance Team, where they are tracked to resolution and reported to national regulatory agencies as required. An independent Data Monitoring Committee reviews safety and other relevant data at regular meetings.

Following a risk assessment according to UK Medicines and Healthcare products Regulatory Agency (MHRA) guidelines, the trial is classified as category B (risk somewhat higher than standard medical care). A risk-adapted monitoring plan has been adopted, compliant with Good Clinical Practice (ICH E6 (R2)) and MHRA guidelines. Trial monitoring is conducted via a combination of central data monitoring (for data quality and completeness), supplemented by scheduled and triggered on-site monitoring visits and remote tele-monitoring (phone and video-conferencing visits).

**Table 1.** Inclusion criteria.

| |
|---|
| 1. Age $\geq$40 years |
| 2. Non-severe ischaemic stroke (modified Rankin score $\leq$3) or high-risk TIA (ABCD2 $>$ 3, or any ABCD2 score with positive DWI or cranio- cervical artery stenosis $\geq$50% in appropriate/ipsilateral arterial territory) |
| 3. Onset of qualifying stroke/TIA later than 72 hours and 28 days before randomisation |
| 4. Qualifying stroke/TIA probably caused by large artery stenosis, lacunar disease, or cryptogenic embolism in opinion of treating physician, based on initial assessment and data |
| 5. Glomerular filtration rate $>$50 mL/minute |

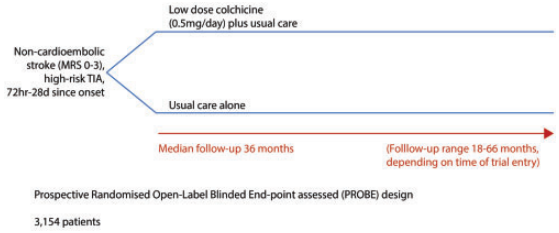


**Figure 1.** Schematic of design of CONVINCE.

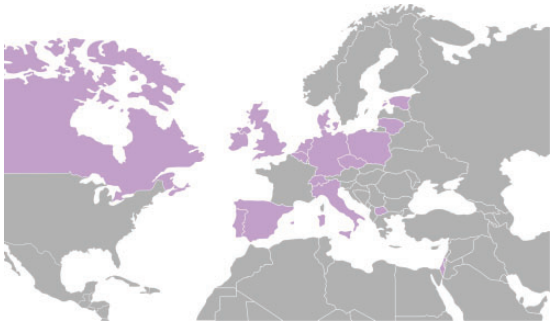

**Figure 2.** Map of countries participating in CONVINCE (shaded in purple).

## Sample size estimation

The original sample size for CONVINCE was 2630 participants. Following the Vanguard Stage and a review of outcome rates reported in recent randomised trials and registry studies, the sample size was increased to 3154 subjects as a precaution to ensure adequate statistical power. The revised sample size is designed to detect a 25% risk reduction (relative hazard 0.755 after accounting for a 15% rate of colchicine non-adherence) after a median follow up period of 36 months, corresponding to rates of the primary

outcome of 13.5% in the control arm and 10.26% in the colchicine-treated arm (power 80%, 5% two-sided significance level).

### *Provisional statistical analysis plan*

The analysis of primary outcome will be by intention-to-treat analysis, including patients lost to follow-up or censored due to death. A between-group comparison of time to primary outcome will be done using the log-rank test. The between-group effect size will be analysed by Cox proportional hazards modelling, adjusting for minimisation variables, expressed as the hazard ratio and confidence intervals. This analysis will be repeated in the 'on-treatment' group, after exclusion of patients who are non-adherent to colchicine. Secondary analyses of safety, secondary outcomes (including cognition/disability), and health economics (direct resource costs and health outcomes, QALY-adjusted using the EQ5D-5L) will be done. The effect of colchicine on the overall primary outcome stratified by key pre-specified subgroups with tests for interaction will be analysed. A detailed statistical and health economic analysis plan will be published prior to database lock.

## Discussion

Despite recent advances in emergency treatment, the global burden of stroke continues to increase due to increasing life-expectancy and increasing incidence in low- and middle-income countries.[19] Survivors of previous stroke or TIA are at particularly high risk for second stroke and adverse outcomes such as disability, dementia, and death. In population studies and hospital registries, one-fifth to one-quarter of all stroke events are recurrent events. In a recent systematic review, in studies which included patients after 2005 (in the era of modern stroke preventive treatment), the annual combined rate of recurrent stroke, myocardial infarction and vascular death was 6.6% in stroke survivors, equating to about 30% at 5 years.[1] In the Oxford Vascular Study, the 5-year risk of recurrent stroke or acute coronary events was 25% (lacunar stroke), 27% (cryptogenic stroke), and 33% (large artery and cardio-embolic stroke).[20] Depending on subtype, one-quarter to one-half of these recurrent events are fatal. Prevention of such recurrent events is an urgent priority to improve the medium and long-term outcome of patients following stroke and TIA.

Data from epidemiological studies and randomised trials supports an important role for atherosclerosis in the pathogenesis of first and recurrent events in large artery, lacunar, and cryptogenic stroke subtypes. For example, prognostic scores which mainly comprise risk factors for atherosclerosis (such as the Essen Risk Score) predict recurrent stroke and coronary events regardless of initial stroke subtype.[21] In the SPARCL trial, anti-atherosclerotic lipid-lowering therapy with atorvastatin reduced recurrent ischaemic stroke and coronary events in patients with non-cardioembolic stroke, without effect modification by stroke subtype.[9] In the FOURIER trial, patients with ischaemic stroke of all subtypes had benefit from anti-atherosclerotic lipid-lowering treatment with evolocumab, a proprotein subtilisin/kexin convertase type 9 inhibitor.[22]

A large body of experimental and clinical evidence supports a role for inflammation in atherosclerotic plaque instability and clinical stroke events. Blood inflammatory markers such as C-reactive protein and interleukin-6 predict first and recurrent stroke, including in patients with lacunar stroke enrolled in the SPS3 trial.[23–25] Mendelian randomisation studies, which eliminate reverse causation, have demonstrated increased stroke risk with enhanced MCP-1 expression, and stroke protection with reduced IL-6 signalling.[26,27] Pathological studies have demonstrated robust associations of carotid plaque inflammation with cap rupture (the precipitating event for thrombo-embolism) and early recurrent stroke in symptomatic patients. Imaging studies using FDG-positron emission tomography (a marker of macrophage infiltration) have demonstrated that carotid plaque inflammation predicts early stroke recurrence.[28]

In coronary patients, randomised trials of anti-inflammatory treatments reported reduced recurrent vascular events. In CANTOS, canukinumab (an IL-1B antagonist) reduced recurrent events in patients with coronary disease, with greatest benefit in those with highest on-treatment CRP and IL-6 reduction.[29,30] However cost and safety considerations (increased risk of fatal sepsis) are likely to preclude routine use of canukinumab for long-term vascular prevention. In the LoDoCo and COLCOT trials, low-dose colchicine reduced recurrent events in coronary patients already treated with background modern preventive therapy.[14,15] A meta-analysis of stroke outcomes in coronary trials reported a 69% pooled risk reduction for stroke (although limited by few stroke outcomes).[16]

Colchicine is an orally-administered, inexpensive, pleiotropic anti-inflammatory agent with a long history of clinical use and established safety profile at low doses. Originally derived from the crocus plant, colchicine inhibits tubulin aggregation and microtubule function, reducing inflammatory cell motility, mitosis, inflammasome activation and IL-1B activation, with secondary reductions in IL-6 and other key cytokines.[12,13] A Cochrane systematic review identified no serious adverse effects of low-dose (0.5-1.0mg)

colchicine in trials of patients with vascular disease.[31] The safety of long-term low-dose colchicine is supported by data from the 2 completed coronary trials, where the most common adverse effects were transient reversible nausea and diarrhoea. In COLCOT, a small increase in pneumonia was reported in the colchicine arm (0.9% versus 0.4% in placebo arm). No other signal suggesting increased susceptibility to infection has emerged to date and it is unclear whether this was due to chance.

In a recent Cochrane systematic review of randomised trials of anti-inflammatory therapy for secondary stroke prevention, a search of over 33,000 publications returned CONVINCE as the only current or published trial addressing this question.[32] Given the importance of prevention of recurrent events in stroke survivors, if the trial hypothesis is proven correct (a 25% relative risk reduction with colchicine treatment), the future benefits may be substantial. The impact in populations will depend on external generalisability in clinical practice, and the extent of uptake of colchicine treatment. About 85% of strokes are ischaemic, and approximately two-thirds of these are non-cardioembolic. The eligibility criteria for CONVINCE are deliberately wide to maximize generalisability of the findings, with appropriate precautions for safety reasons as the patient sample is expected to be older than in coronary trials. Therefore, the results will be applicable to a high proportion of stroke/TIA patients in practice. Because colchicine is inexpensive and already approved by regulatory agencies for other indications, it is likely that uptake into clinical practice would be adopted with little delay. It is also likely to be cost-effective. CONVINCE is powered to detect an absolute risk reduction of at least 3% (relative-risk reduction 25%, number-needed-to-treat 33), equating to an estimated cost of €1220 per year to prevent one stroke.

CONVINCE is under way in 113 sites in Europe and Canada, with an estimated 150 sites to be participating by mid-2020. Over 1500 patients have been randomised, with recruitment of the remaining patients and follow-up due to be completed by 2023. Outcome rates and tolerability are in line with assumptions and no significant safety concerns have been identified by the Data Monitoring Committee. If the trial hypothesis is confirmed, CONVINCE may provide a new strategy for vascular prevention following stroke and TIA, in addition to anti-thrombotic, lipid-lowering, anti-hypertensive, and other measures in current use.

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## Ethical approval

In place at all recruiting sites.

## Informed consent

Provided by all patients.

## Guarantor

PK.

## Contributorship

All authors were contributors to protocol development, gaining ethical approval, patient recruitment, study procedures, and data management. PK wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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